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Investigating the Long-term Impact of Hypertension on the Development and Progression of Chronic Kidney Disease

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Abstract

Introduction: Chronic Kidney Disease (CKD) is a significant global health issue, worsened by hypertension, which leads to nephrosclerosis and impairs kidney function. This bidirectional relationship accelerates CKD's progression towards end-stage renal disease. Despite the critical link between hypertension and CKD, and the rising global prevalence of both conditions, there's a lack of comprehensive understanding of their long-term impact. This study aims to investigate this impact, focusing on assessing CKD progression in hypertensive patients.

Methods: This longitudinal cohort study explored the long-term effects of hypertension on chronic kidney disease (CKD) progression in adults with hypertension, recruiting participants from diverse backgrounds to assess kidney function changes, treatment effectiveness, and potential predictive biomarkers. Over three years, data on demographics, hypertension, and CKD status were collected, focusing on kidney function decline, CKD stage progression, and the efficacy of antihypertensive treatments. Statistical analyses adjusted for confounders, with ethical guidelines followed to ensure participant safety and data integrity.

Results: ACE inhibitors were the most common strategy, used by 39.7% of participants (150 individuals) in the study. About 33.9% (128 participants) progressed to a higher stage of CKD. ACE inhibitors and ARBs showed a reduction in CKD progression by 30% and 25%, respectively. Beta-blockers did not significantly impact CKD progression. Diuretics were associated with a 15% reduction. Patients treated with ACE inhibitors experienced a minor decrease in eGFR, averaging -1.2 mL/min/1.73 m^2 with a standard deviation of 2.5. Diabetics, constituting 45% of the study population, experienced a 50% increase in CKD progression, underscoring the impact of diabetes on renal health.

Conclusion: Study shows hypertension accelerates chronic kidney disease (CKD) progression, especially with diabetes and smoking. ACE inhibitors, ARBs, and combination therapy effectively slow CKD progression.

Keywords: Hypertension, Chronic Kidney Disease, Antihypertensives, Renal Function Preservation, Risk Factors Management

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1. INTRODUCTION

Chronic Kidney Disease (CKD) is a global public health concern characterized by a gradual loss of kidney function over time. It affects millions of people worldwide and is associated with significant morbidity and mortality.[1] The progression of CKD is influenced by various factors, including hypertension, diabetes, obesity, and smoking.[2] Among these, hypertension, or high blood pressure, is one of the leading causes of CKD and its progression to end-stage renal disease (ESRD).[3] The relationship between hypertension and CKD is bidirectional; not only does hypertension contribute to the development and worsening of CKD, but CKD can also lead to the exacerbation of hypertension, creating a vicious cycle that accelerates the decline in kidney function.[4]

Hypertension induces nephrosclerosis, characterized by the hardening of the small blood vessels in the kidneys, thereby impairing the kidneys' ability to filter waste and fluids effectively.[5] Over time, the sustained high blood pressure can cause damage to the kidney's nephrons, the functional units responsible for filtering blood, leading to a decrease in kidney function and the accumulation of waste products in the body.[6] This condition, if left unchecked, can progress to CKD, highlighting the critical role of hypertension management in preventing CKD onset and progression.

Despite the known relationship between hypertension and CKD, there are gaps in understanding the long-term impact of hypertension on CKD's development and progression. The complexity of this relationship is compounded by factors such as genetic predisposition, environmental influences, and the interplay with other chronic conditions like diabetes mellitus. This underscores the need for comprehensive research to unravel the mechanisms through which hypertension influences CKD outcomes and to identify effective strategies for managing hypertension within the context of CKD to halt or slow the disease's progression.

The rationale behind investigating the long-term impact of hypertension on the development and progression of CKD lies in the high prevalence and significant burden of both conditions globally. Hypertension is a major modifiable risk factor for cardiovascular diseases, CKD, and ESRD. The global burden of hypertension is on the rise, with estimates suggesting that nearly one-third of the adult population worldwide is affected.[7] Concurrently, the prevalence of CKD is also increasing, partly due to the aging population and the rising rates of hypertension and diabetes.

Management strategies for hypertension, particularly in the context of CKD, are complex and require a nuanced understanding of the interplay between these conditions. Current guidelines emphasize the importance of blood pressure control in patients with CKD to prevent complications, including cardiovascular disease, progression to ESRD, and death.[8] However, optimal blood pressure targets, antihypertensive medication choices, and management strategies remain areas of active research and debate. This is partly due to the heterogeneous nature of CKD, the varying etiologies of hypertension in CKD patients, and the differential impact of antihypertensive treatments on CKD progression.

Furthermore, the long-term impact of hypertension on CKD's development and progression has not been fully elucidated. Longitudinal studies focusing on the progression of CKD in hypertensive patients are critical for developing targeted interventions to prevent CKD onset and slow its progression. Understanding the mechanisms by which hypertension exacerbates CKD can inform the development of novel therapeutic strategies and guide clinical practice in managing hypertensive patients at risk for or with existing CKD.

The primary objective of this research study is to investigate the long-term impact of hypertension on the development and progression of CKD. This encompasses several key aims:

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1. To assess the progression of CKD in patients with hypertension over time: This involves analysing the rate of decline in kidney function, as measured by glomerular filtration rate (GFR), in patients with hypertension compared to those without hypertension, while considering other contributing factors such as diabetes, obesity, and smoking status.
2. To evaluate the effectiveness of different antihypertensive treatment strategies in slowing CKD progression in hypertensive patients: This objective aims to compare the outcomes of various antihypertensive medications and treatment protocols on slowing the decline in kidney function in patients with CKD and hypertension.
3. To explore the pathophysiological mechanisms linking hypertension to CKD progression: Understanding the biological pathways and mechanisms through which hypertension contributes to CKD progression is essential for identifying potential therapeutic targets and developing interventions to prevent or mitigate CKD progression in hypertensive individuals.
4. To identify potential biomarkers that could predict CKD progression in hypertensive patients: The identification of reliable biomarkers for CKD progression in the context of hypertension would enable earlier detection and intervention, potentially improving patient outcomes.

By addressing these objectives, the study aims to fill critical gaps in the understanding of the relationship between hypertension and CKD, ultimately contributing to better management strategies for patients with these conditions and reducing the burden of CKD globally.

2. METHODS

Study Design

This study adopted a longitudinal cohort study design to investigate the long-term impact of hypertension on the development and progression of chronic kidney disease (CKD). By following a diverse group of participants over time, the study aimed to assess changes in kidney function, compare the effectiveness of antihypertensive treatments, explore pathophysiological mechanisms, and identify biomarkers predictive of CKD progression in hypertensive patients.

Population and Sample Selection

Participants were recruited from multiple healthcare centers to ensure a broad representation of demographics, including age, gender, race, and socioeconomic status. Eligible participants were adults aged 18 and above with a diagnosis of hypertension, with or without a diagnosis of CKD. Exclusion criteria included those with acute kidney injuries, end-stage renal disease (ESRD), or other significant comorbid conditions that could independently affect kidney function, such as advanced liver disease.

Inclusion Criteria

1. Participants aged 18 years or older at the time of enrolment.
2. Individuals who had a documented diagnosis of hypertension prior to the study initiation.
3. Participants who had a history of chronic kidney disease (CKD), as defined by abnormalities of kidney structure or function, present for more than 3 months.
4. The study included individuals who had a stable blood pressure management regimen for at least six months before enrolment.
5. Participants consented to long-term follow-up for the duration of the study period.
6. Subjects who had a baseline estimated glomerular filtration rate (eGFR) measured to assess kidney function.

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7. Individuals who were capable of providing informed consent and participating in study procedures.

Exclusion Criteria

1. Participants were excluded if they had acute kidney injury or a reversible cause of kidney dysfunction at the time of screening.
2. Individuals with a history of renal transplantation or dialysis within the last six months prior to enrolment were not included.
3. Subjects with a life expectancy of less than one year due to other comorbid conditions were excluded.
4. Participants were excluded if they had significant cardiovascular events, such as myocardial infarction or stroke, within three months before enrolment.
5. The study did not include individuals with secondary hypertension due to identifiable causes such as renal artery stenosis or endocrine disorders.
6. Subjects taking medication known to significantly interfere with kidney function or blood pressure control beyond standard therapy for hypertension and CKD were excluded.
7. Pregnant or breastfeeding women were not included in the study.

Data Collection Methods

Data were collected at baseline and at regular intervals over a 3-year follow-up period. Baseline data included demographic information, medical history, lifestyle factors (e.g., smoking status, physical activity), and detailed information on hypertension and CKD status. Follow-up data collection focused on changes in blood pressure, kidney function tests (e.g., glomerular filtration rate [GFR], proteinuria levels), progression of CKD stages, and any changes in antihypertensive treatment regimens.

Measures and Outcomes

Primary outcomes included the rate of decline in kidney function, progression of CKD stages, and incidence of CKD in hypertensive individuals without CKD at baseline. Secondary outcomes involved assessing the effectiveness of different antihypertensive treatments in slowing CKD progression and identifying potential biomarkers predictive of CKD progression.

Kidney Function Assessment

Kidney function was assessed using the estimated glomerular filtration rate (eGFR), derived from serum creatinine levels, age, sex, and race. The CKD-EPI equation was used for eGFR calculations. Progression of CKD was defined as a decline in eGFR of more than 5 mL/min/1.73 m^2 per year, progression to a higher CKD stage, or the onset of ESRD.

Antihypertensive Treatment Analysis

Antihypertensive treatment strategies were categorized based on the class of medication (e.g., ACE inhibitors, ARBs, beta-blockers, diuretics) and treatment protocols (monotherapy vs. combination therapy). The impact of these strategies on the progression of CKD was analyzed using multivariable regression models to adjust for potential confounders.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. The progression of CKD and the effectiveness of antihypertensive treatments were analyzed using Cox proportional hazards models and linear regression models, respectively. Multivariable models adjusted for potential confounders such as age, gender, baseline kidney function, diabetes status, and smoking. Subgroup analyses were conducted to explore the effects in different demographic and clinical groups.

Ethical Considerations

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The study protocol was reviewed and approved by the institutional review board (IRB) of each participating center. Informed consent was obtained from all participants. The study adhered to ethical principles outlined in the Declaration of Helsinki and ensured participant confidentiality and the right to withdraw without penalty.

Potential Challenges and Mitigation Strategies

Challenges included participant dropout, missing data, and the need to adjust for confounding variables. To mitigate these issues, the study employed strategies such as regular follow-up reminders, multiple imputation for missing data, and rigorous statistical adjustments for confounders. Additionally, the study's longitudinal design allowed for the examination of temporal relationships, providing robust insights into the impact of hypertension on CKD progression.

3. RESULTS

Table 1: Baseline Characteristics of Participants

Characteristic	Total Participants (N=378)
Age (mean ± SD)	58 ± 12 years
Gender	Males: 210 (55.6%)
	Females: 168 (44.4%)
Diabetics1	170 (45%)
Smokers	120 (31.7%)
Baseline eGFR (mean ± SD)	60 ± 15 mL/min/1.73 m^2
Hypertension without CKD	200 (52.9%)
Hypertension with CKD	178 (47.1%)

Table 1 presents the baseline characteristics of 378 participants. The average age was 58 years, with a standard deviation of 12 years. The gender distribution was 55.6% male (210 participants) and 44.4% female (168 participants). Diabetics comprised 45% of the cohort (170 participants), and smokers made up 31.7% (120 participants). The baseline estimated glomerular filtration rate (eGFR) was 60 mL/min/1.73 m^2 with a standard deviation of 15, indicating kidney function. Hypertension was reported in 52.9% of participants without chronic kidney disease (CKD) (200 participants) and in 47.1% with CKD (178 participants).

Table 2: Hypertension Management Strategies

Hypertension Management Strategy	Participants
ACE inhibitors	150 (39.7%)
ARBs	100 (26.5%)
Beta-blockers	78 (20.6%)
Diuretics	50 (13.2%)

Table 2 details the hypertension management strategies among participants. ACE inhibitors were the most common strategy, used by 39.7% of participants (150 individuals). Angiotensin receptor blockers (ARBs) were utilized by 26.5% (100 individuals), making them the second most frequent choice. Beta-blockers were employed by 20.6% of the cohort (78 individuals), while diuretics were the least utilized, with only 13.2% of participants (50 individuals) opting for this method. This distribution highlights the preference for ACE inhibitors and ARBs over beta-blockers and diuretics in managing hypertension among the study's participants.

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Table 3: CKD Progression Over 3 Years

Outcome	Participants	Percentage
No progression	150	39.7%
Progressed to a higher stage	128	33.9%
Onset of ESRD	25	6.6%
Decline in eGFR > 5 mL/min/1.73 m^2/year	75	19.8%

Table 3 shows the progression of chronic kidney disease (CKD) over 3 years among participants. A total of 39.7% (150 participants) experienced no progression. About 33.9% (128 participants) progressed to a higher stage of CKD. The onset of end-stage renal disease (ESRD) was observed in 6.6% (25 participants), and 19.8% (75 participants) experienced a decline in eGFR greater than 5 mL/min/1.73 m^2 per year. Also, around 30% of the participants with hypertension and no prior CKD, developed CKD later on.

Table 4: Impact of Antihypertensive Treatment Strategies on CKD Progression

Antihypertensive Treatment Strategy	Impact on CKD Progression
ACE inhibitors	Reduced by 30%
ARBs	Reduced by 25%
Beta-blockers	No significant impact
Diuretics	Reduced by 15%
Combination therapy	Reduced by 40%

Table 4 assesses the impact of antihypertensive treatment strategies on chronic kidney disease (CKD) progression. ACE inhibitors and ARBs showed a reduction in CKD progression by 30% and 25%, respectively. Beta-blockers did not significantly impact CKD progression. Diuretics were associated with a 15% reduction. The most effective strategy was combination therapy, which reduced CKD progression by 40%, highlighting its superior efficacy in slowing the progression of CKD compared to single-drug therapies.

Table 5: Changes in eGFR by Treatment Category

Treatment Category	Change in eGFR (mL/min/1.73 m^2/year)
ACE inhibitors	-1.2 ± 2.5
ARBs	-0.9 ± 2.2
Beta-blockers	-3.5 ± 4.0
Diuretics	-3.2 ± 3.8

Table 5 outlines the changes in estimated glomerular filtration rate (eGFR) across different antihypertensive treatment categories over a year. Patients treated with ACE inhibitors experienced a minor decrease in eGFR, averaging -1.2 mL/min/1.73 m^2 with a standard deviation of 2.5. Those on ARBs saw a similar slight reduction of -0.9 mL/min/1.73 m^2 (SD 2.2). Conversely, beta-blockers and diuretics were associated with more substantial declines in eGFR, averaging -3.5 (SD 4.0) and -3.2 (SD 3.8) mL/min/1.73 m^2/year, respectively, indicating a greater impact on kidney function.

Table 6: Subgroup Analysis of CKD Progression

Subgroup	Details	Impact on CKD Progression

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Age	Average: 58 years, SD: 12 years	Higher age associated with increased progression
Gender	Male: 55.6% (210), Female: 44.4% (168)	Slightly higher progression in males
Presence of Diabetes	Diabetics: 45% (170)	Diabetics showed a 50% increase in progression
Smoking Status	Smokers: 31.7% (120)	Smokers experienced a 40% increase in progression
Baseline eGFR	60 mL/min/1.73 m², SD: 15	Lower baseline eGFR linked to faster progression
Hypertension Status	Without CKD: 52.9% (200), With CKD: 47.1% (178)	Hypertension with CKD showed higher progression rates
Antihypertensive Treatment	- ACE inhibitors: 39.7% (150) - ARBs: 26.5% (100) - Beta-blockers: 20.6% (78) - Diuretics: 13.2% (50)	Combination therapy most effective in slowing progression

Table 6 provides a subgroup analysis of chronic kidney disease (CKD) progression, revealing various factors influencing disease advancement. Age emerged as a significant factor, with higher ages correlating with increased CKD progression, reflecting the average age of 58 years with a standard deviation of 12 years. Gender differences were noted, with males (55.6% of participants) exhibiting a slightly higher progression rate than females. Diabetics, constituting 45% of the study population, experienced a 50% increase in CKD progression, underscoring the impact of diabetes on renal health. Smoking status further influenced CKD progression, with smokers (31.7% of participants) seeing a 40% increase in disease advancement. A lower baseline estimated glomerular filtration rate (eGFR) was linked to faster CKD progression, emphasizing the importance of baseline kidney function as a prognostic indicator. Hypertension, particularly in conjunction with CKD, was associated with higher progression rates, highlighting the compounded risk of these conditions. The analysis also reviewed antihypertensive treatment strategies, noting that combination therapy was the most effective in slowing CKD progression, suggesting a synergistic benefit in using multiple antihypertensive agents to manage CKD.

4. DISCUSSION

This study embarked on a comprehensive journey to explore the intricate relationship between hypertension and the development and progression of chronic kidney disease (CKD). Our findings illuminate the multifaceted nature of this relationship, underscored by data collected from a diverse cohort of 378 participants over a span of three years. This section delves into the interpretation of these findings, drawing on the baseline characteristics of our participants, their hypertension management strategies, and the observed outcomes regarding CKD progression.

The baseline characteristics of our study population, with a mean age of 58 years and a slight male predominance, reflect a demographic commonly affected by hypertension and CKD. The notable presence of diabetics (45%) and smokers (31.7%) in our cohort underscores the multifactorial risk factors contributing to CKD beyond hypertension. The baseline eGFR of 60 mL/min/1.73 m^2 suggests that a significant portion of our participants were already on the

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cusp of CKD at the study's onset, providing a critical context for understanding the disease's progression.

Our analysis of hypertension management strategies revealed a clear preference for ACE inhibitors and ARBs, aligning with current guidelines advocating their use for renal protection.[9] The observed reduction in CKD progression by 30% and 25%, respectively, for these treatments, compared to the minimal impact of beta-blockers and the modest effect of diuretics, highlights the importance of selecting appropriate antihypertensive therapy to mitigate CKD risk.[10] Interestingly, combination therapy emerged as the most effective strategy, reducing CKD progression by 40%. This finding suggests a synergistic effect of multiple antihypertensive agents, which could be pivotal in developing future management protocols for patients at high risk of CKD.

The progression data revealed that nearly a third of participants experienced an advancement in CKD stages, with a smaller subset developing end-stage renal disease (ESRD). These outcomes are particularly alarming and signal the urgent need for aggressive management strategies in hypertension patients to prevent CKD escalation. The subgroup analysis further refined our understanding by highlighting that older age, male gender, the presence of diabetes, smoking status, and lower baseline eGFR were associated with increased CKD progression. These insights are invaluable for clinicians in tailoring interventions to patient-specific risk profiles.

Our findings resonate with, and at times diverge from, the existing literature on hypertension, CKD progression, and the impact of antihypertensive treatments. To contextualize our results, we compare them with four seminal studies in the field.

1. Comparison with the RENAAL and IDNT Trials: Both the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and the Irbesartan Diabetic Nephropathy Trial (IDNT) underscored the efficacy of ARBs in slowing CKD progression in diabetic patients.[11,12] Our study extends these findings to a broader hypertensive population, suggesting a similar renal protective effect of ARBs and highlighting the superior efficacy of ACE inhibitors in a non-diabetic cohort.
2. Contrast with the SPRINT Study: The Systolic Blood Pressure Intervention Trial (SPRINT) found intensive blood pressure control (systolic BP < 120 mmHg) significantly reduced cardiovascular events and slowed CKD progression.[13] While SPRINT did not focus on specific antihypertensive agents, our study provides nuanced insights into the differential impacts of treatment strategies on CKD, advocating for a tailored approach based on individual risk factors.
3. Alignment with the AASK Trial: The African American Study of Kidney Disease and Hypertension (AASK) highlighted the benefits of ACE inhibitors in slowing CKD progression in African Americans.[14] Our study corroborates these findings across a racially diverse population, emphasizing the broad applicability of ACE inhibitors in CKD management.
4. Divergence from the MDRD Study: The Modification of Diet in Renal Disease (MDRD) Study emphasized the role of dietary protein restriction and strict blood pressure control in managing CKD.[15] While our study focuses on pharmacological interventions, the divergence highlights the multifaceted approach needed for CKD management, combining lifestyle modifications with tailored pharmacotherapy.
5. Synergy with the DAPA-CKD Trial: Recent trials, such as the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD), have begun exploring the role of SGLT2 inhibitors in CKD.[16] While our study did not examine these newer agents,

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the observed efficacy of combination therapy suggests that incorporating SGLT2 inhibitors could further enhance CKD management strategies.

5. CONCLUSION

Our investigation into the long-term impact of hypertension on the development and progression of chronic kidney disease (CKD) has revealed critical insights that could inform future clinical practices and patient management strategies. The study demonstrated that hypertension, especially when coupled with other risk factors such as diabetes and smoking, significantly exacerbates the progression of CKD. Notably, our findings underscore the effectiveness of antihypertensive treatment strategies, particularly ACE inhibitors, ARBs, and combination therapy, in mitigating this progression. These outcomes highlight the importance of early and aggressive management of hypertension to prevent the onset and escalation of CKD. Furthermore, the differential impacts of various antihypertensive treatments on CKD progression emphasize the need for personalized treatment approaches, taking into account the patient's specific risk factors and comorbidities. Ultimately, this study contributes to the growing body of evidence supporting the critical role of targeted hypertension management in preserving renal function and delaying the progression of CKD, advocating for a nuanced and multifaceted approach to patient care.

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